# Synthesis and σ Binding Properties of 1′- and 3′-Halo- and 1′,3′-Dihalo-*N*-normetazocine Analogues

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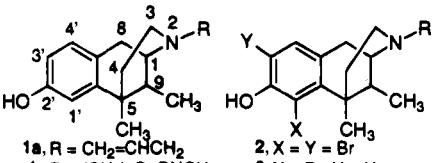
The synthesis and σ1 and σ2 binding properties of several 1′- and 3′-halo- and 1′,3′-dihalo-substituted analogues of (+)-*N*-benzyl- and (+)- and (−)-*N*-dimethylallyl-*N*-normetazocine are presented. Structure–activity relationship analyses of the binding data showed that halogen substitution at the 1′-position of these *N*-substituted *N*-normetazocine analogues had little effect on σ1 binding affinity, whereas 3′-halo substitution as well as 1′,3′-dihalo substitution resulted in a reduction of affinity. σ2 affinity was increased by the presence of a 3′-bromo substituent in this series of (+)-*N*-substituted *N*-normetazocines.

Compounds from several structural classes have been reported to bind with high affinity to σ receptors. σ pharmacophore models have been proposed based on the structure–activity relationship (SAR) studies on several individual compound classes.[1-11] However, the wide variety of structures that bind to σ receptors has made it difficult to identify a unique pharmacophore. This is complicated further by the identification of two σ receptors, σ1 and σ2. Since (±)-*N*-allyl-*N*-normetazocine (**1a**, SKF 10,047) was the first σ ligand and (+)-pentazocine [(+)-**1b**] has proven to be one of the most useful tools to study this receptor, our own studies have been directed toward an SAR study of 6,7-benzomorphan class of σ ligands. For example, we reported that σ1 binding potency of a number of (+)- and (−)-*N*-substituted *N*-normetazocines (**1**, R = various substituents) was highly sensitive to changes in the *N*-substituent and the absolute stereochemistry of the normetazocine.[2,3] (+)-*N*-Benzyl-*N*-normetazocine [(+)-**1c**] with a $K_i$ of 0.67 nM possessed the highest affinity for the σ1 site. In addition, (+)-**1c** showed high selectivity for the σ1 site relative to σ2 site or relative to the μ-opioid and PCP receptor.[2,12] A quantitative structure–activity relationship (QSAR) study showed that the binding potency of a series of (+)-*cis*-*N*-(*para*-, *meta*-, and *ortho*-substituted benzyl)-*N*-normetazocines [(+)-**1d**, X = various substituents] were correlated with the size and location of the benzyl substituent.[13] In this paper, we present the synthesis and σ receptor binding properties of 1′-halo, 3′-halo, and 1′,3′-dihalo analogues of (+)-**1c** as well as (+)- and (−)-pentazocine (compounds **2**–**7**, R = benzyl or dimethylallyl).




**1a**, R = $CH_2$=$CHCH_2$
**b**, R = $(CH_3)_2C$=$CHCH_2$
**c**, R = $C_6H_5CH_2$
**d**, R = $XC_6H_4CH_2$

**2**, X = Y = Br
**3**, X = Br, Y = H
**4**, X = H, Y = Br
**5**, X = H, Y = I
**6**, X = Y = Cl
**7**, X = Cl, Y = H

## Chemistry

All of the target compounds **2**–**7** can be prepared using (+)- and (−)-*N*-normetazocine[14] (**8**) as the starting material (Scheme 1). Treatment of **8** with pyridine perbromide hydrobromide in acetic acid or iodine–potassium iodide in 2 N sodium hydroxide gives the 3′-bromo- and 3′-iodo-*N*-normetazocine analogues, **9** and **10**, respectively. Chlorination with sulfuryl chloride in acetic acid gives the 1′,3′-dichloro-*N*-normetazocine (**11**), whereas bromination with 2 equiv of bromine in acetic acid containing triethylamine gives 1′,3′-dibromo-*N*-normetazocine (**12**). Catalytic dehydrohalogenation of **11** and **12** using 10% palladium on carbon catalyst in methanol yields the 1′-chloro- and 1′-bromo-*N*-normetazocines **13** and **14**, respectively. Alkylation of (+)-**8**–**14** with benzyl bromide in dimethylformamide containing potassium hydrogen carbonate gives the (+)-*N*-benzyl analogues (+)-**2a**–**7a**. Reductive alkylation of (+)- and (−)-**9**, (+)- and (−)-**10**, and (+)-**12**–**14** with 3-methylbutenal and sodium cyanoborohydride in methanol yields the *N*-dimethylallyl analogues (+)- and (−)-**4b**, (+)- and (−)-**5b**, (+)-**2b**, (+)-**3b**, and (+)-**7b**, respectively.

The structural assignments for compounds **2**–**7** were based on elemental analyses of the hydrochloride salts and $^1$H NMR analyses of the free bases. The $^1$H NMR spectra of the 3′-halo analogues showed singlet resonances for the 1′- and 4′- hydrogen, the 1′-halo analogues showed two doublets for the 3′- and 4′-halogen, and the 1′,3′-dihalo analogues showed only one singlet for the 4′-hydrogen (Table 1).

## Results and Discussion

Table 2 lists the σ binding data for 1′- and 3′-halo- and 1′,3′-dihalo-substituted analogues of (+)-*N*-benzyl-*N*-normetazocine [(+)-**1c**] as well as (+)- and (−)-pentazocine [(+)-**1b** and (−)-**1b**, respectively]. The *N*-benzyl-1′,3′-dibromo and 1′,3′-dichloro analogues (+)-**2a** and (+)-**6a**, respectively, as well as the *N*-(dimethylallyl)-1′,3′-dibromo analogue, (+)-**2b**, showed much lower σ1 $K_i$ values than the parent compounds (+)-**1c** and (+)-

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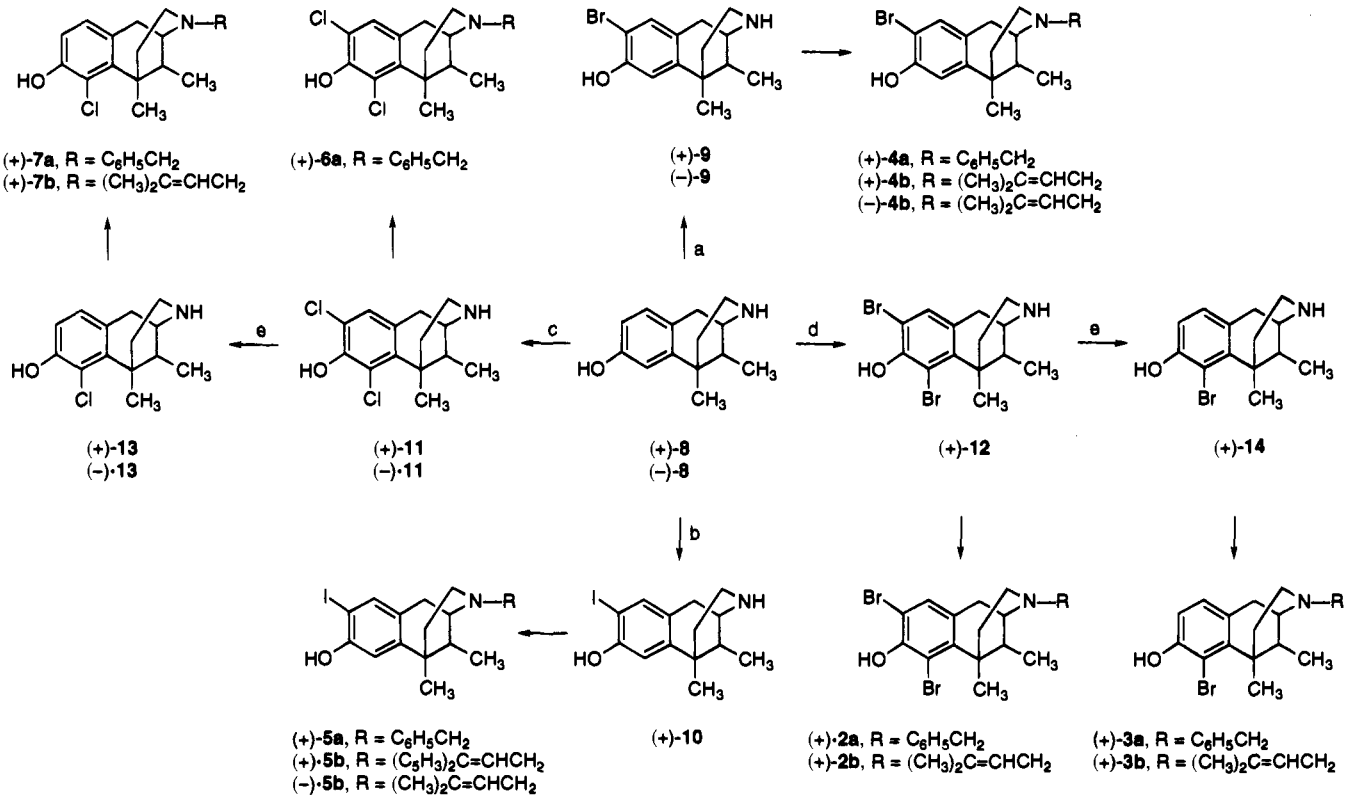
**Scheme 1**[a]




[a] (a) $C_5H_5N{\cdot}Br_2{\cdot}HBr$, HOAc; (b) $I_2$, KI, 2 N NaOH; (c) $SO_2Cl_2$, HOAc; (d) $Br_2$ (2 equiv), HOAc, $Et_3N$; (e) 10% Pd/C, $H_2$, $CH_3OH$.

**Table 1.** Selected $^1H$ NMR Data for **2**–**7** Free Bases in $CDCl_3$[a]

| | $^1H$ NMR Resonances | | | |
|---|---|---|---|---|
| compd | 1′ | 3′ | $J_{3'4'}$ | 4′ |
| (+)-**2a** | | | | 7.24 |
| (+)-**2b** | | | | 7.25 |
| (+)-**3a** | | 6.80[b] | 8.3 | 6.90[b] |
| (+)-**3b** | | 6.83[b] | 8.3 | 6.97[b] |
| (+)-**4a** | 6.80 | | | 7.25 |
| (+)-**4b** | 6.84 | | | 7.20 |
| (−)-**4b** | 6.82 | | | 7.20 |
| (+)-**5a** | 6.93 | | | 7.42 |
| (+)-**5b** | 6.85 | | | 7.40 |
| (−)-**5b** | 6.78 | | | 7.40 |
| (+)-**6a** | | | | 7.08 |
| (+)-**7a** | | 6.83 | 8.5 | 6.96 |
| (+)-**7b** | | 6.85 | 8.5 | 7.40 |

[a] Chemical shifts are reported as $\delta$ values in parts per million (ppm) relative to $Si(CH_3)_4$ at 250 MHz. [b] These assignments could be reversed.

**1b**, respectively. $\sigma 2$ binding affinity of (+)-**2b** was increased 7-fold, but little change in $\sigma 2$ binding affinity was noted for (+)-**2a** and (+)-**6a**. Monobromination and monoiodination of (+)-**1c** and (+)-pentazocine [(+)-**1b**] at the 3′-position [(+)-**4a**, (+)-**5a**, (+)-**4b**, and (+)-**5b**, respectively] resulted in analogs with lower affinity for $\sigma 1$ and no effect or slightly higher affinity for $\sigma 2$. In contrast, monobromination and monochlorination of (+)-**1c** and (+)-pentazocine [(+)-**1b**] at the 1′-position [(+)-**3a**, (+)-**7a** and (+)-**3b**, (+)-**7b**] had little effect on the $\sigma 1$ $K_i$ values. Compounds (+)-**3a**, (+)-**7a**, and (+)-**3b** possessed increased affinity for $\sigma 2$, whereas (+)-**7b** was much weaker at $\sigma 2$. Since (+)-**7a** and (+)-**7b** differ only in their *N*-substitution, the reason for the difference in $\sigma 2$ binding is not apparent. Monobromination and monoiodination of (−)-pentazocine [(−)-**1b**] at the 3′-position [(−)-**4b** and (−)-**5b**] resulted in a 2-fold increase in $\sigma 1$ binding affinity and a 2–3-fold loss in binding at the $\sigma 2$ receptor.

In summary, synthetic methods were developed for the synthesis of 1′- and 3′-monohalo- and 1′,3′-dihalo-substituted analogues of *N*-substituted *N*-normetazocines. Halogen substituted in the 1′-position of *N*-substituted *N*-normetazocine had little effect on $\sigma 1$ binding affinity, whereas 3′-substitution and 1′,3′-disubstitution resulted in a reduction of affinity. This suggests that there may be steric restriction for binding at the 3′-position. In contrast, the 1′-position appears not to show such a steric restriction. Thus, further modification at the 1′-position could lead to interesting $\sigma 1$ ligands.

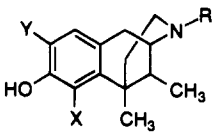
## Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). NMR spectra were recorded on a Bruker WM-250 spectrometer using tetramethylsilane as internal standard. Thin-layer chromatography was carried out on Whatman silica gel 60 plates using hexane–$Et_2O$–$Et_3N$ (10:9:1) as eluent. Visualization was accomplished under UV illumination or in an iodine chamber. Microanalyses were carried out by Atlantic Microlab, Inc., Norcross, GA.

**(+)-2-Benzyl-1′,3′-dibromo-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan [(+)-2a].** To a stirred solution of (+)-**8** (119 mg, 0.55 mmol) and triethylamine (177 mg, 1.64 mmol) in glacial acetic acid (12 mL) under nitrogen at room temperature was added a solution of bromine in glacial acetic acid (12 mL) dropwise over a 10 min period. The reaction mixture was stirred further for 10 min and poured into a mixture of ice and excess ammonium hydroxide. The precipitate was filtered slowly, washed with water, and air-dried to give 174 mg of (+)-**12**.

A mixture of (+)-**12** (174 mg, 0.46 mmol), benzyl bromide (85.5 mg, 0.5 mmol), and potassium bicarbonate (200 mg) in

**Table 2.** Sigma Binding Data for 1′-Halo-, 3′-Halo-, and 1′,3′-Dichloro-Substituted-*N*-Normetazocines




| | | | | $K_i$ (nM)[a] | | | | |
|---|---|---|---|---|---|---|---|---|
| compd | X | Y | R | σ1 [$^3$H] pentazocine | ±SEM | σ2 [$^3$H]DTG | ±SEM | σ2/σ1[b] ratio |
| (+)-**1c** | H | H | $C_6H_5CH_2$ | 0.67 | 0.1 | 1710 | 407 | 2600 |
| (+)-**2a** | Br | Br | $C_6H_5CH_2$ | 70.6 | 3.45 | 2010 | 202 | 28 |
| (+)-**3a** | Br | H | $C_6H_5CH_2$ | 1.75 | 0.18 | 346 | 37.5 | 200 |
| (+)-**4a** | H | Br | $C_6H_5CH_2$ | 68.6 | 1.69 | 1220 | 148 | 18 |
| (+)-**5a** | H | I | $C_6H_5CH_2$ | 231 | 15.4 | 597 | 29.6 | 2.6 |
| (+)-**6a** | Cl | Cl | $C_6H_5CH_2$ | 71.5 | 10.2 | 2170 | 287 | 30 |
| (+)-**7a** | Cl | H | $C_6H_5CH_2$ | 1.72 | 0.62 | 764 | 115 | 440 |
| (+)-**1b** | H | H | $(CH_3)_2C{=}CHCH_2$ | 3.1 | 0.3 | 1540 | 313 | 500 |
| (+)-**2b** | Br | Br | $(CH_3)_2C{=}CHCH_2$ | 120 | 15.9 | 211 | 10.9 | 1.8 |
| (+)-**3b** | Br | H | $(CH_3)_2C{=}CHCH_2$ | 2.49 | 0.12 | 283 | 29.8 | 110 |
| (+)-**4b** | H | Br | $(CH_3)_2C{=}CHCH_2$ | 114 | 14.5 | 365 | 44.5 | 3.2 |
| (+)-**5b** | H | I | $(CH_3)_2C{=}CHCH_2$ | 944 | 150 | 223 | 3.4 | 0.24 |
| (+)-**7b** | Cl | H | $(CH_3)_2C{=}CHCH_2$ | 2.62 | 0.23 | 4960 | 361 | 1900 |
| (−)-**1b** | H | H | $(CH_3)_2C{=}CHCH_2$ | 83.1 | 6.2 | 36.5 | 5.76 | 0.44 |
| (−)-**4b** | H | Br | $(CH_3)_2C{=}CHCH_2$ | 37.4 | 2.01 | 72.8 | 3.54 | 1.9 |
| (−)-**5b** | H | I | $(CH_3)_2C{=}CHCH_2$ | 35.2 | 3.57 | 94 | 14.4 | 2.7 |

[a] Values are the average ± SEM of two to three experiments. Each experiment was carried out in duplicate. [b] σ2/σ1 are ratios of $K_i$ values.

dimethylformamide (5 mL) under nitrogen was stirred at 50 °C overnight. The reaction mixture was diluted with water (100 mL) and the product extracted with ethyl acetate (3 × 30 mL), dried ($Na_2SO_4$), evaporated, and purified by flash chromatography on silica gel using hexane–ethyl acetate (4:1) as eluent to give (+)-**2a**.

Addition of 1 N ethereal HCl to an ethereal solution of the free base afforded 60 mg (26%) of the HCl salt: mp 185–187 °C; $[\alpha]^{25}_D$ +106.4° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$) δ 0.82 (d, 3, *J* = 7.0 Hz), 1.61–1.73 (m, 1), 1.68 (s), 1.87–2.09 (m, 3), 2.49–2.55 (m, 1), 2.75–3.00 (m, 3), 3.57, 3.67 (2, AB, *J* = 13.4 Hz), 5.02 (bs, 1), 7.24 (s), and 7.25–7.35 (m, s). Anal. ($C_{21}H_{24}Br_2ClNO$): C, H, N.

**(+)-1′,3′-Dibromo-5,9α-dimethyl-2-(3,3-dimethylallyl)-2′-hydroxy-6,7-benzomorphan [(+)-2b].** A mixture of (+)-**12** prepared as above (161 mg, 0.43 mmol), 3-methyl-2-butenal (72.1 mg, 0.86 mmol), and sodium cyanoborohydride (54.1 mg, 0.86 mmol) in methanol (10 mL) was stirred at room temperature under nitrogen overnight. The solvent was removed, and the residual product was diluted with water (20 mL), extracted with ethyl acetate (3 × 30 mL), dried, and evaporated. Flash chromatography on silica gel using ethyl acetate–ether (1:1) as eluent gave pure (+)-**2b**. The addition of a 1 N ethereal HCl to an ethereal solution of (+)-**2b** yielded 41.1 mg (19%) of the hydrochloride salt: mp 150–152 °C; $[\alpha]^{25}_D$ +105.7° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$) δ 0.87 (d, 3, *J* = 7.0 Hz), 1.26 (s, 3), 1.63 (s, 3), 1.71 (s, 3), 1.77–2.05 (m, 4), 2.68 (dd, 1), 2.81–2.86 (m, 1), 2.96 (m, 1), 3.05 (d, 1), 5.25 (t, 1), 5.82 (bs, 1), 7.25 (s, 1). Anal. ($C_{19}H_{26}Br_2ClNO{\cdot}0.75H_2O$) C, H, N.

**(+)-2-Benzyl-1′-bromo-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan [(+)-3a].** A solution of (+)-**12** (100 mg, 0.27 mmol) in methanol (15 mL) containing 10% palladium on charcoal (50 mg) was stirred at room temperature and under an atmosphere of hydrogen gas for 2 h. The catalyst was separated by filtration and washed with methanol. Evaporation of the filtrate gave 96.8 mg of (+)-**12**.

The crude sample of (+)-**12** was converted to (+)-**3a** using a procedure analogous to that described for (+)-**2a** to give 110 mg (96% of product): $^1$H NMR ($CDCl_3$, free base) δ 0.82 (d, 3, *J* = 7.0 Hz), 1.66–1.73 (m, 1), 1.68 (s, 3), 1.86–2.10 (m, 3), 2.47–2.54 (m, 1), 2.75–3.00 (m, 3), 3.56, 3.67 (AB, 2, *J* = 13.3 Hz), 5.77 (bs, 1), 6.80 (d, 1, *J* = 8.3 Hz), 6.90 (d, 1, *J* = 8.3 Hz), 7.11–7.36 (m, 5). The hydrochloride salt was prepared by a procedure analogous to that described for (+)-**2a**: mp 177–180 °C; $[\alpha]^{25}_D$ +130.0° (*c* 1, EtOH). Anal. ($C_{21}H_{25}BrClNO{\cdot}0.25H_2O$) C, H, N.

**(+)-1′-Bromo-5,9α-dimethyl-2-(3,3-dimethylallyl)-2′-hydroxy-6,7-benzomorphan [(+)-3b].** The title compound was prepared by a procedure analogous to that described for the preparation of (+)-**2b**. Thus, (+)-1′-bromonormetazocine [(+)-**14**] (185.8 mg, 0.49 mmol) prepared as above, 3-methyl-2-butenal (62.1 mg, 0.74 mmol), and sodium cyanoborohydride (62.1 mg, 0.99 mmol) was used to prepare (+)-**3b** which was purified by flash chromatography on silica gel using ether–hexane (2:1) as the eluent. The HCl salt was prepared as described for (+)-**2b**, giving 48.2 mg: mp 183–185 °C; $[\alpha]^{25}_D$ 61.2° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) δ 0.87 (d, 3, *J* = 6.6 Hz), 1.24 (s, 3), 1.63 (s, 3), 1.72 (s, 3), 1.77–2.04 (m, 4), 2.61–2.74 (m, 1), 2.81–2.86 (m, 1), 2.93–2.95 (m, 2), 3.08 (d, 2), 5.26 (t, 1); 5.65 (bs, 1), 6.83 (d, 1, *J* = 8.3 Hz), 6.97 (d, 1, *J* = 8.3 Hz). Anal. ($C_{19}H_{27}BrClNO{\cdot}0.5H_2O$) C, H, N.

**(+)-2-Benzyl-3′-bromo-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan [(+)-4a].** A mixture of (+)-**8** (330 mg, 1.5 mmol) and pyridinium perbromate (535.3 mg, 1.7 mmol) in glacial acetic acid was stirred at 80 °C under nitrogen for 1.5 h. Saturated potassium carbonate solution was added until the solution was basic (pH 11). After dilution with water, the resulting precipitate was separated by filtration, washed with water, and dried to afford 416 mg (86%) of (+)-**9**.

Compound (+)-**9** (207 mg, 0.7 mmol) was converted to (+)-**4a** by a procedure analogous to that described for (+)-**2a** to give 127.8 mg (46%) of (+)-**4a**·HCl: mp 192–194 °C; $[\alpha]^{25}_D$ +88.9° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) δ 0.77 (d, 3, *J* = 7.1 Hz), 1.19–1.28 (m, 1), 1.25 (s, 3), 1.77 (dt, 1, *J* = 4.8, 12.7 Hz), 1.87–1.92 (m, 1), 2.10 (dt, 1, *J* = 3.1, 12.4 Hz), 2.45–2.51 (m, 1), 2.62 (dd, 1, *J* = 5.7, 18.3 Hz), 2.87–3.03 (m, 2), 3.60, 3.71 (AB, 2, *J* = 13.3 Hz), 6.80 (s, 1), 7.21–7.38 (m, 6, aromatic). Anal. ($C_{21}H_{25}BrClNO{\cdot}0.5H_2O$) C, H, N.

**(+)- and (−)-3′-Bromo-5,9α-dimethyl-2-(3,3-dimethylallyl)-2′-hydroxy-6,7-benzomorphan [(+)-4b and (−)-4b].** Using a procedure analogous to that described for (+)-**2b**, (+)-3′-bromonormetazocine [(+)-**9**] (161 mg, 0.54 mmol) prepared as described above, 3-methyl-2-butenal (91.4 mg, 1.09 mmol), and sodium cyanoborohydride (68.7 mg, 1.09 mmol) were used to prepare (+)-**4b**, which was purified by flash chromatography on silica gel using ether–hexane (2:1) as eluent. The HCl salt was prepared as described for (+)-**2b** to give 73 mg (34%): mp 159–161 °C; $[\alpha]^{25}_D$ 88.0° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) δ 0.82 (d, 3, *J* = 7.0 Hz), 1.29 (s, 3), 1.65 (s, 3), 1.71 (s, 3), 1.76–2.10 (m, 4), 2.55–2.68 (m, 1), 2.87–3.0 (m, 3), 3.12 (d, 2, *J* = 6.9 Hz), 5.26 (t, 1), 6.13 (bs, 1), 6.84 (s, 1), 7.20 (s, 1). Anal. ($C_{19}H_{27}BrClNO$) C, H, N.

Compound (−)-**4b** was prepared by a procedure exactly analogous to that described for (+)-**4b**. The HCl salt: mp 158–160 °C; $[\alpha]^{25}_D$ −87° (*c* 0.12, EtOH). Anal. ($C_{19}H_{27}BrClNO\cdot 0.5H_2O$) C, H, N.

**(+)-2-Benzyl-5,9α-dimethyl-2′-hydroxy-3′-iodo-6,7-benzomorphan [(+)-5a].** A solution of iodine (1.02 g) and potassium iodide (1.02 g) in water (35 mL) was added dropwise to a stirred solution of (+)-**8** (434 mg, 2 mmol) in 2 N sodium hydroxide (13 mL) and water (22 mL). After stirring for 10 min, the reaction mixture was neutralized with dry ice, and the yellowish precipitate was separated by filtration, washed with water, and dried to give 650 mg of (+)-**10**: $^1$H NMR ($CDCl_3$, free base) δ 0.77 (d, 3, *J* = 7.0 Hz), 1.18–1.27 (m, 1), 1.21 (s, 3), 1.77 (dt, 1, *J* = 4.8, 12.7 Hz), 1.86–1.91 (m, 1), 2.10 (dt, 1, *J* = 3.0, 12.3 Hz), 2.45–2.51 (m, 1), 2.61 (dd, 1, *J* = 5.8, 18.3 Hz), 2.87–3.03 (m, 2), 3.61, 3.71 (AB, 2, *J* = 13.3 Hz), 5.25 (bs, 1), 6.73 (s, 1), 6.93–7.37 (m, 5), 7.42 (s, 1).

A 160 mg (0.34 mmol) sample of (+)-**10** was converted to (+)-**5a** using a procedure analogous to that described for (+)-**2a**. The HCl salt: mp 194–197 °C; $[\alpha]^{25}_D$ +67.4° (*c* 1, EtOH). Anal. ($C_{21}H_{25}ClINO$) C, H, N.

**(+)- and (−)-5,9α-Dimethyl-2-(3,3-dimethylallyl)-2′-hydroxy-3′-iodo-6,7-benzomorphan [(+)-5b and (−)-5b].** Using a procedure analogous to that described for (+)-**3b**, a 160 mg (0.34 mmol) sample of (+)-**10**, 3-methyl-2-butenal (57 mg, 0.68 mmol), and sodium cyanoborohydride (43 mg, 0.68 mmol) was converted to 80 mg (50%) of (+)-**5b**·HCl: mp 190–192 °C; $[\alpha]^{25}_D$ +52.5° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) δ 0.83 (d, 3, *J* = 7.0 Hz, $CH_3$), 1.32 (s, 3), 1.67 (s, 3), 1.74 (s, 3), 1.85–2.12 (m, 4), 2.60–2.70 (m, 1), 2.87–3.0 (m, 3), 3.16 (d, 2, *J* = 6.9 Hz), 5.30 (t, 1, $CH_2CH$), 6.85 (s, 1, aromatic H), 7.40 (s, 1). Anal. ($C_{19}H_{27}ClINO\cdot H_2O$) C, H, N.

The enantiomer (−)-**5b**·HCl was prepared in 51% yield by an analogous procedure: mp 182–184 °C; $[\alpha]^{25}_D$ −47.5° (*c* 0.12, EtOH). Anal. ($C_{19}H_{27}ClINO\cdot 0.75H_2O$) C, H, N.

**(+)-1-Benzyl-1′,3′-dichloro-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan [(+)-6a].** To a stirred solution of (+)-**8** (217 mg, 1 mmol) in glacial acetic (10 mL) under nitrogen at room temperature was added sulfuryl chloride (270 mg, 2 mmol) dropwise and the reaction mixture stirred overnight. After removal of the solvent, the crude (+)-11 was converted to (+)-**6a** using a procedure analogous to that described for (+)-**2a** to give 165 mg (35%) of (+)-**6a**·HCl: mp 172–173 °C; $[\alpha]^{25}_D$ 111.4° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) 0.86 (d, 3, *J* = 7.0 Hz), 1.64 (s, 3), 1.69–1.76 (dd, 1), 1.80–1.89 (m, 2), 1.97–2.07 (dt, 1), 2.47–2.53 (m, 1), 2.76–2.97 (m, 3), 3.56, 3.68 (AB, 2, *J* = 14.4 Hz), 7.08 (s, 1), 7.20–7.56 (m, 5). Anal. ($C_{21}H_{24}Cl_3NO$) C, H, N.

**(+)-1-Benzyl-1′-chloro-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan [(+)-7a].** A solution of (+)-**13** prepared from 434 mg (2.0 mmol) of (+)-**8** in methanol (25 mL) containing 10% palladium on charcoal (300 mg) was stirred at room under one atmosphere of hydrogen gas for 48 h. The catalyst was separated by filtration, washed with methanol, and evaporated to afford (+)-**13**.

The crude (+)-**13**·HCl (300 mg, 1.04 mmol) was converted to 118 mg (15%) of **7a**·HCl using dimethylformamide (10 mL), benzyl bromide (267.2 mg, 1.6 mmol), and potassium bicarbonate (200 mg): mp 160–162 °C; $[\alpha]^{25}_D$ 107.9° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) δ 0.85 (d, 3, *J* = 7.0 Hz), 1.65 (s, 3), 1.70–1.77 (dd, 1), 1.80–1.89 (m, 2), 2.0–2.09 (dt, 1), 2.46–2.53 (m, 1), 2.73–2.99 (m, 3), 3.57, 3.69 (AB, 2, *J* = 14.4 Hz), 6.83 (dd, 1), 6.96 (dd, 1), 7.19–7.47 (m, 5). Anal. ($C_{21}H_{25}Cl_2NO\cdot 0.25H_2O$) C, H, N.

**(+)-1′-Chloro-5,9α-dimethyl-2-(3,3-dimethylallyl)-2′-hydroxy-6,7-benzomorphan [(+)-7b].** Using a procedure analogous to that described for (+)-**2b**, a 240 mg (0.83 mmol) sample of (+)-**13**, 3-methyl-2-butenal (198.3 mg, 1.66 mmol), and sodium cyanoborohydride (148.8 mg, 1.66 mmol) gave 77 mg (25%) of (+)-**7b**·HCl: mp 148–150 °C; $[\alpha]^{25}_D$ 114.3° (*c* 1, EtOH); $^1$H NMR ($CDCl_3$, free base) δ 0.87 (d, 3, *J* = 7.0 Hz), 1.65 (s, 3), 1.68 (s, 3), 1.72 (s, 3), 1.76–2.03 (m, 4), 2.57–2.63 (m, 1), 2.71–2.96 (m, 3), 3.08 (d, 2, *J* = 6.9 Hz), 5.26 (t, 1), 6.85 (d, 2), 7.40 (d, 1). Anal. ($C_{19}H_{27}Cl_2NO\cdot 0.25H_2O$) C, H, N.

**σ1 and σ2 Binding Assays.** σ1 binding sites were labeled using the σ1-selective ligand [$^3$H]-(+)-pentazocine and guinea pig brain membranes, and σ2 sites were labeled using [$^3$H]-DTG in the presence of dextrallorphan to mask σ1 sites in rat liver membranes.[12]

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